REMARKS

I. Response to Restriction Requirement:

Applicants note that the Restriction Requirement mailed July 1, 2004 has been vacated and replaced with the Restriction Requirement set forth in the instant Office Action.

The Office Action states that claims 1-31, drawn to nucleotides, nucleotide constructs and methods requiring the use of nucleotides or nucleotide constructs, contain more than one individual, independent, and distinct nucleotide sequence in alternative form. For this reason, the Office Action required restriction of the claimed invention to a single nucleotide sequence.

Applicants understand this Requirement to mean that Applicants are to elect a single nucleotide sequence with respect to each of claims 1 and 22. Accordingly, Applicants provisionally elect, with traverse, **SEQ ID NO: 28,** with respect to claim 1, and **SEQ ID NO: 38,** with respect to claim 22. Applicants gratefully note that the Examiner has indicated that he will examine claim 21 directed to **SEQ ID NOS: 119-130** on the merits (*see,* Office Action, para. bridging pp. 2-3).

Applicants respectfully assert that the Restriction Requirement is improper as it applies to the requirement that a single HCV oligonucleotide be elected. In particular, Applicants assert that there would be no undue burden on the Examiner to search more than one HCV oligonucleotide.

Indeed, MPEP § 803.04 states that "to further aid the biotechnology industry in protecting its intellectual property without creating an undue burden on the Office, the Commissioner has decided *sua sponte* to...permit a reasonable number of nucleotide sequences to be claimed in a single application...(and that)....it has been determined that normally ten sequences constitute a reasonable number for examination purposes" (emphases added). This section of the MPEP goes on to state that "in some exceptional cases, the complex nature of the claimed material, for example a protein amino acid sequence reciting three dimensional folds, may necessitate that the reasonable number of sequences to be selected be less than ten" (emphasis added).

The instant Restriction Requirement states only that "[t]he USPTO frequently restricts examination to one elected sequence" (*see*, Office Action, page 2, third paragraph). The Office Action provides no reasoning as to why the USPTO cannot search more than the single HCV sequence. Applicants respectfully note that the oligonucleotide sequences in question are only 20-30 nucleotides in length and are readily searchable using the computer algorithms and sequence databases available to the USPTO. Applicants further note that, even if the search were "complex" in nature (which is denied), MPEP § 803.04 does not state that this is an issue in examining multiple sequences, rather, it states that the complexity of the claimed material may be an issue in some exceptional cases, however the sequences claimed are not complex and a justification for their exceptional treatment has not been presented. Furthermore, Applicants note that the mere fact that the sequences each have a "distinct nucleotide sequence" is not dispositive to whether it would be an undue burden to examine them together. This is particularly true in the instant case where a simple search for all possible HCV antisense sequences could be conducted simply and efficiently by using a single oligonucleotide search string (namely, the HCV target mRNA sequence provided in Figure 1 of the application-as-filed). Accordingly, Applicants respectfully urge reconsideration of the Restriction Requirement and withdrawal of the requirement to elect a single HCV oligonucleotide sequence. If the Examiner is willing to reconsider this Requirement and expand his search to cover at least ten HCV oligonucleotide sequences, then Applicants would like to elect **SEQ ID NOS: 26, 27, 28, 29, 31, 33, 36, 37, 47, and 68** with respect to claim 1 and **SEQ ID NOS: 38, 29, 40, 41, 42, 43, 44, 45, 46, and 48** with respect to claim 22, for further examination on the merits.

With respect to claims 42-45, the Office Action states that because these claims are drawn to compositions reciting different combinations of individual nucleotide sequences, Applicants are required to select one combination for examination.

Accordingly, Applicants provisionally elect the combination of **SEQ ID NOS: 28 and 68**, with traverse.

Applicants note that the Office Action mistakenly notes that Applicants have already elected the combination of SEQ ID NOS: 28 and 38 for examination. While it is true, that

Applicants elected SEQ ID NOS: 28 and 38 in response to the last Restriction Requirement (of July 1, 2004), Applicants note that they were not elected in response to a Restriction Requirement with respect to claim 42. Indeed, Applicants respectfully draw the Examiner's attention to the fact that claim 42 depends on claim 1, and claim 1 does not recite SEQ ID NO: 38. Accordingly, it would be improper for Applicants to elect the combination of SEQ ID NOS: 28 and 38 with respect to claims 42-45.

Applicants also note that the Office Action, in seeming contradiction to the requirement for election of one combination of sequences, states, in relevant part, that "[i]f the selected combination contains ten or fewer sequences, all of the sequences of the combination will be searched. If the selected combination contains more than ten sequences, the combination will be searched until one nucleotide sequence is found to be allowable" (*see*, Office Action, page 2, fourth paragraph). Thus, Applicants understand this to mean that the Examiner should consider at least ten combinations of HCV oligonucleotides.

Indeed, Applicants respectfully assert that it would not pose an undue burden on the USPTO to examine at least ten combinations of two different HCV sequences with respect to claim 42. In fact, the Office Action raises no argument concerning any burden on the Patent Office to search ten combinations of HCV oligonucleotides. Accordingly, Applicants respectfully request reconsideration of the instant Requirement with respect to claims 42-45. If the Examiner is willing to consider ten combinations of HCV sequences, then Applicants would like to elect **SEQ ID NOS: 27 and 28; 28 and 29; 28 and 68; 28 and 119; 28 and 125; 28 and 128; 28 and 129; 28 and 131; 47 and 80; and 29 and 68** for further examination on the merits.

II. Information Disclosure Statement:

With respect to the PTO-1449 submitted with the Information Disclosure Statement of February 6, 2004, Applicants note that the Examiner has crossed out several references. However, Applicants also note that these references have been considered by the Examiner and were crossed out by the Examiner only because they were already of record in the instant application.

III. Amendments to the Specification:

The specification has been amended to correct minor clerical and/or typographical errors. In addition, as requested by the Examiner, the address for the American Type Culture Collection (ATCC) has been corrected.

No new matter has been added by way of the instant amendments to the specification.

IV. Amendments to the Claims:

Claims 1-31 and 42-46 are pending in the instant application.

Claims 7, 23, 24, 26, 29, 31, and 46 are withdrawn from further consideration without prejudice pursuant to 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention. Applicants reserve the right to prosecute these claims at a later date.

Claims 1, 2, 4, 5, 21, 22, 25, 27, 30 and 42 have been amended in the instant Amendment. Support for the amendment to claim 2 can be found, for example, at the paragraph bridging pages 12 and 13, page 32, and Figure 1 of the application as filed. Support for the amendment to claim 30 can be found in Table 1E at pages 29-30 of the application as filed. The other claim amendments are either deletions of subject matter or typographical/clerical changes. No new matter has been added by way of the instant amendments to the claims.

V. Rejections under 35 U.S.C. § 112, second paragraph:

Claims 1-6, 8-22, 25, 27, 28, 30 and 42-45 stand rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite for the reasons described below (*see*, Office Action, page 3, seventh paragraph).

(a) Claims 1, 22 and 42-45 were alleged to claim more than was elected. Claims 1, 22 and 42 have been amended to recite the elected sequence(s). Accordingly, this rejection has been rendered moot.

(b) The Examiner rejected claims 1, 2, 4, 5, 8 and 43 for allegedly being indefinite for the recitation of the term "synthetic oligonucleotide."

Applicants respectfully traverse this rejection and assert that the term "synthetic oligonucleotide" is a term of art, which is well understood by those of ordinary skill in the relevant art. This is evidenced by the abstracts of two articles, published before the filing date of the instant application, both of which use this term (*see*, **Appendix A**). Furthermore, Applicants note that "synthetic oligonucleotide" is defined in the paragraph bridging pages 10 and 11 of the application as filed. For the foregoing reasons, Applicants respectfully request reconsideration of this rejection and withdrawal of the same.

(c) Claims 1, 21, and 22 were purported to be incomplete because they refer to tables in the specification. Claims 1, 21, and 22 have been amended to delete reference to tables in the specification. Accordingly, this rejection has been rendered moot.

(d) Claims 4 and 5 were rejected for lacking antecedent basis for the phrase "the 5' untranslated region." Claims 4 and 5 have been amended to recite, in relevant part, "a 5' untranslated region." Accordingly, the grounds for this rejection have been rendered moot.

(e) Claim 21 stands rejected as allegedly being mis-descriptive because the sequences listed in the claim are not complementary to two or more non-contiguous regions of the HCV genome or HCV messenger RNA as required by claim 2.

Applicants note that claim 21 has been amended to be in independent format. Accordingly, this rejection has been rendered moot.

(f) The Examiner rejected claim 25 as purportedly being indefinite for recitation of "self-stabilized by a loop."

Applicants respectfully assert that at the time of the filing of the instant application one of ordinary skill in the art was aware of what is meant by the term "self-stabilized by a loop." This is evidenced by the article entitled "Self-stabilized antisense oligodeoxynucleotide phosphorothioates: properties and anti-HIV activity" attached herewith as **Appendix B**, and which was cited in the application as filed in the context of describing self-stabilized oligonucleotides (*see*, page 18, lines 6-17 of the application as filed). Accordingly, Applicants respectfully request reconsideration of this rejection and withdrawal of the same.

(g) Claim 27 stands rejected for lacking antecedent basis for the recitation of "the molecule." Claim 27 has been amended to recite, in relevant part, "a molecule." Accordingly, the grounds for this rejection have been rendered moot.

(h) Claim 30 stands rejected for lacking antecedent basis for the recitation of "at least one additional triplex-forming strand." Applicants note that claim 30 has been amended to recite, in relevant part, "at least one triplex-forming sequence selected from the group consisting of 3'GGGGG5', 3'CCCCC5', 3'CCCCCCCUCCC5', and 3'CCUCCC5'." Accordingly, Applicants respectfully aver that the ground for this rejection has been overcome.

VI. Rejections under 35 U.S.C. § 112, first paragraph:

(a) Claims 2-6, 8-20, 25, 27, 28, 30, 43, and 45 stand rejected under 35 U.S.C. § 112, first paragraph, for purportedly failing to comply with the written description requirement (*see,* Office Action, para. bridging pp. 4-5).

Without acquiescing to this rejection, and solely to expedite prosecution of this application, independent claim 2 has been amended to recite, "A synthetic oligonucleotide comprising a sequence complementary to at least two non-contiguous regions of an HCV messenger or genomic RNA, wherein one of the at least two non-contiguous regions is complementary to a 5' untranslated region of the HCV messenger or genomic RNA, and wherein one of the at least two non-contiguous regions is complementary to a region selected from the group consisting of a 5' untranslated region of the HCV messenger or genomic RNA, and a region within +1 to +48 of the HCV messenger or genomic RNA."

Applicants have provided more than adequate written description support for the claimed invention in the instant application. For example, the specification at page 12, line 22 to page 14, line 13 provides a description of numerous non-contiguous oligonucleotides encompassed by the invention. In addition, Tables 1C, 1D, 1E and Table 2 provide the specific sequences of numerous species of non-contiguous oligonucleotides that fall within the scope of the claimed invention.

Applicants note that the written description requirement does not require that every possible species that is encompassed by a given claim be recited in the specification. Rather, as noted above, all that is required is that a representative number of species be described.

Because Applicants' specification provides the structure of numerous species that are encompassed by the pending claims as amended, Applicants respectfully aver that they have met the written description requirement. Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. § 112, first paragraph (written description) as to independent claim 2, and claims 3-6, 8-20, 25, 27, 28, 30, 43 and 45, which are dependent on claim 2, and thus have all the limitations thereof, be reconsidered and withdrawn.

(b) Claims 2-6, 8-20, 25, 27, 28, 30, 43, and 45 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly being non-enabling (*see*, Office Action, page 5, first full para.).

Applicants remind the Examiner that independent claim 2 has been amended to recite, "A synthetic oligonucleotide comprising a sequence complementary to at least two non-contiguous regions of an HCV messenger or genomic RNA, wherein one of the at least two non-contiguous regions is complementary to a 5′ untranslated region of the HCV messenger or genomic RNA, and wherein one of the at least two non-contiguous regions is complementary to a region selected from the group consisting of a 5′ untranslated region of the HCV messenger or genomic RNA, and a region within +1 to +48 of the HCV messenger or genomic RNA."

Applicants respectfully contend that they have provided adequate enablement for the claimed invention as amended. According to MPEP § 2164.01, the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). This section of the MPEP also notes, importantly, that the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

Applicants note that the specification as filed provides sufficient guidance regarding:

(i) numerous species of HCV oligonucleotides that fall within the scope of the claimed invention (*see*, above);

(ii) methods of making such oligonucleotides (*see*, for example, Examples 1,and 2, pages 58-62 of the application as filed);

(iii) methods of evaluating oligonucleotides as antisense inhibitors of HCV using four cellular assay systems namely,

(a) inhibition of HCV luciferase fusion protein expression,

(b) inhibition of HCV RNA expression,

(c) inhibition of HCV protein expression, and

(d) RNase H cleavage assays (see, page 31, lines 1-16; page 36, line 4 to page 38, line 27; page 43, lines 1 to 21; and Examples 5, 6 and 7); and

(iv) methods of using these oligonucleotides (see, page 52, line 29 to page 58, line 3).

Thus, the application as filed provides sufficient guidance to one of ordinary skill in the art to make and use the currently claimed invention without undue experimentation. Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. § 112, first paragraph (enablement), as to independent claim 2, and claims 3-6, 8-20, 25, 27, 28, 30, 43 and 45, which are dependent on claim 2, and thus have all the limitations thereof, be reconsidered and withdrawn.

VII. Rejections under 35 U.S.C. § 102(b):

Claims 1, 8, and 12 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Sheridan *et al.* (WO 93/13224), because Sheridan discloses an oligonucleotide of 33 nucleotides in length that includes the 20 nucleotides of SEQ ID NO:28.

Independent claim 1 has been currently amended to recite, "A synthetic oligonucleotide complementary to a portion of the 5' untranslated region of hepatitis C virus and having a nucleotide sequence consisting of SEQ ID NO: 28."

The transitional phrase "consisting of," expressly limits the sequence encompassed by claim 1 to be no more than, and no less than the 20-mer identified as SEQ ID NO:28. Because Sheridan does not teach each and every element of Applicants' claimed invention, Sheridan does not anticipate Applicants' claimed invention.

Based on the foregoing, Applicants respectfully request that this rejection under 35 U.S.C. § 102(b) of independent claim 1, and claims 8 and 12 which are dependent on claim 1 and thus contain all the limitations thereof, be reconsidered and withdrawn.

VIII. Rejections under 35 U.S.C. § 103(a):

Claims 13-21, 25, 27, 28, 30, 42, and 44 were rejected under 35 U.S.C. § 103(a) as purportedly being unpatentable over Sheridan *et al.* (*supra*) in view of Applicants' admitted state of the prior art (page 16, line 19 through page 19, line 29).

Applicants respectfully traverse this rejection.

The Office Action relies on Sheridan for allegedly disclosing an oligonucleotide of 33 nucleotides in length that includes the 20 nucleotides of SEQ ID NO:28. The Office Action purports that Applicants acknowledge that both the use of oligonucleotides as antisense agents as well as modifications of oligonucleotides in antisense oligonucleotides to be old. Based on this position, the Office Action concludes that it would have been obvious to the ordinarily skilled artisan at the time of the invention to use the oligonucleotide of Sheridan as an antisense agent and further to modify moieties within the oligonucleotide to improve its use as an antisense agent (*see,* Office Action, page 6, second para.).

In rejecting claims under 35 U.S.C. § 103, the Examiner bears the initial burden of presenting a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the

claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Sheridan is directed to providing a process for immobilizing nucleic acid probes, including HCV probes, on polystyrene surfaces for use in solution phase nucleic acid sandwich hybridization assays. Nowhere in this reference, and/or in the section of Applicants' specification is there any teaching, suggestion, or motivation regarding the desirability of using any of Sheridan's nucleic acid probes as antisense agents directed to HCV. Importantly, the combined documents cited by the Examiner, provide no teaching or suggestion regarding using Sheridan's oligonucleotides in pharmaceutical compositions as required by Applicants' claims 42 and 44. Furthermore, nowhere in Sheridan or the combined Examiner-cited documents is there any teaching of incorporating ribonucleotides into oligonucleotide probes, as recited in Applicants' claims 13-21, or any teaching of the other limitations recited in Applicants' claims 25, 27, 28 and 30.

Applicants note that the Office Action has provided no reasoning as to why one of ordinary skill in the art would find some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine teachings. Accordingly, there is simply no motivation to combine Sheridan with the alleged teaching in Applicants' specification regarding antisense oligonucleotides to arrive at Applicants' claimed invention.

The Federal Circuit has held that it is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious. *In re Fritch*, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992), citing *In re Gorman*, 933 F.2d 982, 987, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991). To establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the Applicant.

In other words, "there still must be evidence that 'a skilled artisan,...with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *Ecolochem Inc. v. Southern California Edison*, 227 F.3d 1361, 1375, 56 USPQ2d 1065, 1075-76 (Fed. Cir. 2000). The fact that the prior art could have been modified in a manner consistent with Applicants' claims would not have made the modification obvious unless the prior art suggested the desirability of the modification. *In re Gordon*, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984).

Based on the foregoing remarks, Applicants respectfully request reconsideration of this rejection under 35 U.S.C. § 103(a) of claims 13-21, 25, 27, 28, 30, 42, and 44, and withdrawal of the same.

CONCLUSION

Upon entry of the instant amendment, **claims 1-6, 8-22, 25, 27, 28, 30, and 42-45** will be pending and under consideration in the instant application.

In view of the foregoing amendments and remarks, Applicants respectfully submit that this application is now in condition for allowance. If a telephone interview would advance prosecution of the application, the Examiner is invited to call the undersigned at the number listed below.

Applicants petition for a one-month extension of time to reply to the Office Action mailed April 29, 2005. Please charge the requisite fees to our Deposit Account No. 08-0219. In addition, Applicants bring to the Examiner's attention the two additional independent claims in this application. Since there are four independent claims in total, Applicants respectfully request that the USPTO charge the requisite fee of $100.00 for the additional independent claim. Please charge the requisite fees to our Deposit Account No. 08-0219

No other fees are believed to be due in connection with the filing of the response; however, if there are any fees due, please charge the fees to our Deposit Account No. 08-0219.

Respectfully submitted,

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Date: August 17, 2005

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APPENDIX A

Copies of Abstracts of two journal articles published before the filing date of the instant application that evidence that the term "synthetic oligonucleotide" was well-known in the art at the time of filing of the instant application.

APPENDIX B

A copy of the article entitled "Self-stabilized antisense oligodeoxynucleotide phosphorothioates: properties and anti-HIV activity," by Tang *et al.* (*Nucl. Acids Res.* **21**(11):2729-35, 1993) that was cited in the instant application as filed, and which evidences that the phrase "self-stabilized by a loop" was well-known by the ordinarily skilled artisan at the time of filing of the instant application.